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Original Article

Consensus statement on the management of late-onset rheumatoid arthritis

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ABSTRACT

Objectives: Late-onset rheumatoid arthritis (LORA), which has been increasing in recent years, lacks evidence for initial treatment. Japanese rheumatology experts recognized this gap and addressed it by developing consensus statements on the first clinical application of LORA.

Methods: These statements were created following an introductory discussion about treatment fundamentals, which included a review of existing literature and cohort data. The steering committee created a draft, which was refined using a modified Delphi method that involved panel members reaching a consensus. The panel made decisions based on input from geriatric experts, clinical epidemiologists, guideline developers, patient groups, and the LORA Research Subcommittee of the Japan College of Rheumatology.

Results: The consensus identified four established facts, three basic approaches, and six expert opinions for managing LORA. Methotrexate was recommended as the primary treatment, with molecular-targeted agents being considered if treatment goals cannot be achieved. An emphasis was placed on assessing the lives of older patients due to challenges in risk management and methotrexate accessibility caused by comorbidities or cognitive decline.

Conclusions: The experts substantiated and refined 13 statements for the initial treatment of LORA. To validate these claims, the next is to conduct a registry study focusing on new LORA cases.

KEYWORDS: Expert opinion; clinical practice guidelines; late-onset rheumatoid arthritis (LORA); older patient; pharmacological management

Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease characterized by joint inflammation that gradually impairs physical function and daily life. Currently, over 800,000 patients with RA receive treatment in Japan, with 35% of them over the age of 75 years [1, 2]. While RA has

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traditionally manifested between the ages of 30 and 50 years, recent reports have highlighted a surge in late-onset cases [3], raising concerns about a rapid increase in older RA patients, particularly junior baby boomers born in the early 1970s [4].

The landscape of drug therapy for RA has changed significantly since the beginning of the 21st century, allowing for early and comprehensive immunosuppressive treatments to prevent joint destruction. However, the available evidence is primarily derived from randomized controlled trials conducted on patients under the age of 65 years, leaving the initial treatment of patients with late-onset RA (LORA) largely dependent on the experience of individual physicians [5]. When LORA develops in old age, it has several distinct characteristics that set it apart from cases that develop in middle age. There are a higher proportion of male patients and a higher prevalence of negative rheumatoid factor and negative anti-cyclic citrullinated peptide antibodies (ACPA) [5]. Patients with LORA are more likely to require long-term care if adequate treatment is not provided [6], emphasizing the critical need for evidence-based treatment of LORA.

To address this pressing social concern, the Late-onset Rheumatoid Arthritis Registry (LORIS) Study Group was formed by clinical rheumatology experts in Japan, which brings together disciplines such as internal medicine and orthopaedics to treat RA. The panel members who appeared prominently in the 2020 Japan College of Rheumatology (JCR) clinical practice guidelines (CPGs) for managing RA [7] led this research initiative. This study began with the support of a research grant from the Japan Agency for Medical Research and Development in 2021 [4].

This paper describes the process and content of the consensus statement developed by the LORIS study group.

Materials and methods

Steering committee, panel, and advisory board

The steering committee of the panel consisted of a convener, an epidemiologist (M Kojima), and four rheumatologists (T Sugihara, Y Kawahito, T Kojima, and M Harigai). The panel consists of 21 members:13 internists, 7 orthopaedic surgeons, and an epidemiologist including the steering committee members. The advisory board provided guidance and advice for the development of the consensus statement, which had seven individuals. They included two experts in geriatrics, three in clinical epidemiology, one in clinical guideline development, and one board member from the patient organization, Japan Rheumatism Foundation. All panel members declared any potential conflicts of interest they may have before the project began. The first panel meeting took place on 14 January 2023.

Terminology and fundamental concepts

The first phase included a thorough discussion of the basic concept of LORA. To categorize RA occurrences at advanced ages, two common terms were used: 'elderly-onset RA' and 'late-onset RA' (LORA). However, the American Medical Association's recent guidelines discourage the use of terms such as 'aged', 'elder(s)', 'elderly', and 'seniors' when referring to older individuals [8]. This guidance avoided perpetuating the negative stereotypes and discriminatory connotations that are commonly associated with these terms [9]. The Japan Geriatrics Society proposed categorization, with individuals aged 65–74 years classified as 'preold age' and those over 75 years as 'old age' [10]. Consequently, our study used the term 'late' rather than 'elderly' to define LORA patients as those who developed RA at 65 years of age or after the age of 65 years. We applied the term younger-onset RA (YORA) to patients who were under 65 years old in this statement.

Development of statements

The steering committee drafted statements focusing on the management of LORA treatment based on the literature review and secondary analysis of the existing RA cohort data: National Database of Rheumatic Diseases in Japan [3, 11], Institute of Rheumatology, Rheumatoid Arthritis [12], Tsurumai Biologics Communication Registry [13], the Nationwide Inception Cohort of Early Rheumatoid Arthritis Patients in Japan [14], Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) [15, 16], and the Choju registry of RA treated with non-biologic DMARDs and biologics in elderly patients in Japan (CRANE) Study [17, 18]. The statement was structured into three main components: (1) facts, (2) basic approach, and (3) expert opinions on the management of LORA. The draft statements were presented to the panel members at their first face-to-face meeting to kick off discussions on 14 January 2023. The voting phase was then conducted online using a Google Form, an online survey creation tool provided by Google. Following the initial vote, the steering committee made revisions based on the feedback received and distributed the updated draft to the advisory board members for additional insights and recommendations. Following the revision process, the second voting phase was conducted online on 25 March 2023.

Agreement process

The consensus-building process used the modified Delphi method, and the panel members voted on each statement. The consensus statement was finalized when the average score of the evaluations reached at least 7 points. The exact wording was discussed via e-mail and revised until agreement was reached.

External evaluation and approval

The consensus statement was peer-reviewed by the *ad hoc* committee of the JCR for the investigation of LORA, chaired by Prof. Yuko Kaneko of Keio University. The statement was approved finally by the JCR after amending the points raised by the *ad hoc* committee.

The study is limited to the analysis of pre-existing data, and no direct interaction with human subjects occurred. Therefore, all aspects of this research are exempt from ethical review.

Results

FACTs on the management of LORA (Table 1)

The panel members began by reviewing the current situation in Japan to assist healthcare professionals in managing LORA.

The presence of LORA has been increasingly documented [3, 19]. Studies consistently show that patients with LORA have a higher incidence of adverse events than those with YORA [18, 20–24]. Furthermore, data suggest less

Table 1. FACTs on the management of LORA.

	FACTs	Degree of agreement average
1	In recent years, the number of patients developing RA at the age of 65 years (LORA) has increased [3, 19].	8.89
2	Patients with LORA experience more adverse events than those aged ≤65 years [18, 20–24].	8.89
2	Patients with LORA are less likely to receive initial MTX-based therapy compared to patients aged ≤65 years [11, 16].	8.58
4	When DMARDs are appropriately used, patients with LORA are expected to achieve clinical remission the same way that YORA patients do [16, 18, 24, 25].	8.16

Table 2. Basic approach to the management of LORA.

	Basic approach to the management of LORA	Degree of agreement average
1	The management of LORA is determined not only by disease activity but also by chronological age and a comprehensive functional assessment that includes physical function, vitality, depression, cognitive function, activities of daily living, comorbidities, organ damage, and psychological, social, and economic variables.	9
2	When managing LORA, rheumatologists should not pass up opportunities for appropriate treatment adjustments considering comorbidities and patient safety.	9
3	To manage LORA, multidisciplinary medical professionals must provide comprehensive care, including exercise and nutritional guidance.	8.45

methotrexate (MTX) use or molecular-targeted agent use for patients with LORA in contrast to YORA [11, 16]. An analysis combining existing RA cohort data with a literature review revealed that LORA patients had a similar proportion of clinical remission as YORA patients treated with MTX or molecular-targeted agents [16, 18, 24, 25]. However, there was disagreement in consensus over whether to limit the statements to MTX or to include all disease-modifying antirheumatic drugs (DMARDs), resulting in a slightly lower level of agreement among experts.

Basic approach to the management of LORA (Table 2)

The panel members then summarized the fundamental concepts that are required for shared understanding among patients, their families, and healthcare professionals as a basic approach to the management of LORA.

The first statement emphasizes the importance of a comprehensive assessment that considers not only physical and mental aspects but also social and economic factors. Tailoring appropriate treatment for older patients entails evaluating individual comorbidities and conducting a comprehensive functional assessment that measures the state of body and mind, with a focus on biological age as a reflection of the frailty level rather than chronological age alone [5]. Frailty, characterized by declining physical and mental vitality with age, is a precursor to potential long-term care needs [26, 27]. The geriatric specialists of the advisory board recommended that terms like frailty, sarcopenia [28–30], and cachexia [31] be included in the statement. Given the lack of established methods for assessing these conditions in routine RA clinical practice, we chose not to use specific geriatric terminology, instead focused on a comprehensive assessment. This evaluation includes physical and mental aspects, as well as social and economic considerations, which are central to this statement.

Initially, the mental aspect of the draft statement included 'depression and cognitive function' but did not mention 'vitality'. During discussions, we decided to include vitality and depression as separate terms in the statement. Furthermore, agreement was reached on the critical role of the environment, with a focus on family support, collaboration, and the use of caregiver welfare services in managing LORA effectively.

The second statement emphasizes the critical importance of appropriately adjusting treatment, as inadequate treatment in LORA patients may result in advancing joint destruction, secondary osteoporosis development, reduced activities of daily living, increased cardiovascular events, and a rapid increase in the demand for nursing care.

The JCR *ad hoc* committee emphasized the differences in treatment requirements between LORA patients and YORA, as well as the importance of comprehensive guidance that includes medication, exercise, and dietary considerations (addressing osteoporosis, other musculoskeletal ailments, cardiovascular diseases, and strategies for renal function). Following their recommendations, we introduced the third statement, emphasizing the importance of comprehensive care that includes exercise and nutritional guidance delivered collaboratively by a multidisciplinary team of medical professionals.

Statements one and two received a very high average agreement level of 9, while statement three received an average of 8.45 from the panel members.

Expert opinions on the pharmacological management of LORA (Table 3)

Because the evidence on LORA is limited, panellists summarized the experts' preferred drug approach to LORA at this time, which requires additional evidence for validation.

Expert Opinion one: The use of MTX for older patients with RA was consistent with the recommendation of the 2020 JCR CPGs for the management of RA [32] and supported by the efficacy data from the CRANE cohort [17, 18].

Table 3. Expert opinions on the pharmacological management of LORA.

	Expert opinion on the pharmacological management of LORA	Degree of agreement average
1	In the initial treatment of patients with LORA, it is desirable to start MTX with due consideration for safety and gradually increase the dose to the required amount [17, 18].	8.47
2	In the initial treatment of patients with seronegative LORA with low disease activity, csDMARDs other than MTX may be considered [17].	8.21
3	If MTX is not effective in treating patients with LORA, consider adding a bDMARD with due consideration for safety [18].	8.47
4	For patients with LORA who are receiving csDMARDs other than MTX as initial treatment for safety reasons and are not meeting their treatment goals, adding or switching to a bDMARD may be considered with caution [18].	8.58
5	If csDMARDs are not effective in treating LORA, a JAKi may be considered with caution.	8.16
6	In the initial treatment of patients with LORA, the glucocorticoid dose should be kept to a minimum and discontinued within 6 months whenever possible.	8.37

Expert Opinion two: This viewpoint sparked controversy. While European league against rheumatism (EULAR) recommends MTX for initial therapy of RA whenever possible [33], the American college of rheumatology (ACR) suggests starting with hydroxychloroquine over other conventional synthetic DMARDs (csDMARDs), including MTX, in cases of low disease activity [34]. Analysis of CRANE cohort data revealed that most LORA patients with moderate disease activity, no bone erosions, and ACPA-negative status could be treated with csDMARDs other than MTX [17]. A similar trend was observed in LORA with low-to-moderate disease activity from the KURAMA registry [15], which was shared by study group members (unpublished data). Following discussion, it was agreed that csDMARDs other than MTX could be used as initial treatment if the patients lacked poor prognostic factors.

Expert Opinions three, four, and five: These opinions supported the recommendations in the 2020 JCR CPG for the management of RA [7, 32] and were approved with no specific comments from panel members. However, due to limited treatment evidence for older patients, the level of agreement was slightly lower for Janus kinase inhibitors (JAKi).

Expert Opinion six: The panel had differing opinions on the discontinuation or tapering of gulcocorticoids (GCs). The international community is divided on GC use. While the ACR advises against systematic prescribing of GCs [34], EULAR recommends low-dose, short-term applications of GCs when starting or changing csDMARDs, with tapering and discontinuing GCs as soon as clinically feasible [33, 35]. The consensus of the panel favoured the ACR's position. The rationale for discontinuing GCs within 6 months was consistent with osteoporosis guidelines, which stated that 'the risk of vertebral fracture peaks at 3–6 months [36]'. Everyone agreed that daily GC use should be limited due to the increased risks of infection, osteoporosis, and other side effects.

Finally, all statements achieved an average agreement level greater than 8, indicating significant consensus among the panellists.

Discussion

To address the lack of evidence regarding the management of initial treatment of patients with LORA, consensus statements were developed by clinical rheumatology specialists in Japan. The panellists agreed strongly with these statements.

This is the first global consensus statement on the management of LORA. The number of patients with LORA is expected to rise not only in Japan but also in other advanced-ageing societies. As mentioned in the basic approach, the factors influencing treatment decisions for LORA patients are more diverse than those for YORA patients, and methods for evaluating them are yet to be established. RA treatment includes self-care, pharmacological intervention, rehabilitation, and surgery; however, recent rapid advances in pharmacotherapy have reduced the emphasis on other foundational therapies. Nonetheless, the current statement emphasizes the importance of nutritional and exercise therapies as part of a multidisciplinary approach in the current statement in managing LORA. Clinical research aimed at implementing the aspects outlined in the nonpharmacological basic approach in clinical settings is considered necessary in the future.

Expert opinions on pharmacological treatments included MTX, csDMARD, biological DMARD (bDMARD), JAKi, and GC. All are consistent with the recommendations outlined in the 2020 JCR CPG for RA [7, 32]. Statement of Expert Opinion two listed seronegativity and low disease activity as conditions for csDMARDs other than MTX, but these conditions are not explicitly mentioned in the recommendations for csDMARDs in 2020 JCR CPG for RA. However, the algorithm presented in the 2020 JCR CPGs includes Rheumatoid factor/ACPA positivity (especially high-titre positivity) as a condition for considering more aggressive treatment, indicating no contradiction. Because of the scarcity of evidence for bDMARDs in LORA, Statements of Expert Opinion three and four addressed bDMARDs as a whole rather than specific agents. Evidence on the safety of bDMARD in older patients with RAs, though not specific to LORA, has been gathered through postmarketing surveillance in Japan. When these findings were extrapolated to LORA patients, there was widespread agreement on the importance of caution before and during treatment with bDMARDs, with a focus on safety. Data on the efficacy and safety of JAKi in LORA are extremely limited. However, based on current clinical experience, the panel members decided to continue using JAK inhibitors as a treatment option for LORA. There is a strong need to establish evidence to support this statement. Global agreement on the use of GCs remains divided, and evidence on their optimal duration of use is limited. Symptoms similar to polymyalgia rheumatica may necessitate extended GC use. While not explicitly addressed in this statement, more

research into non-steroidal anti-inflammatory drugs use is needed.

RA patients, because of chronic inflammation, are more likely to develop sarcopenia [29, 30, 37] and are at a higher risk of frailty [37, 38]. Assessment and treatment of frailty and sarcopenia in the clinical setting of RA remain pressing issues. Notably, patients with RA express a strong desire for exercise therapy and rehabilitation to maintain physical function [39], which is emphasized in statement three of the basic approach to the management of LORA. However, the current situation indicates that most facilities do not meet these needs, and established protocols are yet to be developed. The timely implementation of effective intervention methods to prevent frailty in patients with RA is critical, especially given the urgent demand for exercise therapy and rehabilitation expressed by patients with RA.

To validate these claims, we launched the LORIS study, a registry of new LORA cases [4]. This study substantiates and refines the consensus statements for the management of LORA.

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Conflict of interest

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